

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)



CLAIMS

We claim:

1. An isolated polypeptide comprising at least a portion of the amino acid sequence of SEQ ID NO:4.
2. The isolated polypeptide of Claim 1, wherein said portion comprises a region comprising at least one tyrosine.
3. The isolated polypeptide of Claim 1, wherein said portion comprises a region defined by amino acids 28 to 233.
4. A purified antibody which binds specifically to a polypeptide comprising at least a portion of the amino acid sequence of SEQ ID NO:4.
5. The purified antibody of Claim 4, wherein said antibody is a polyclonal antibody.
6. The purified antibody of Claim 4, wherein said antibody is a monoclonal antibody.
7. An isolated polynucleotide encoding the polypeptide comprising the sequence of SEQ ID NO:4.
8. The isolated polynucleotide of Claim 7, wherein said polynucleotide comprises the sequence of SEQ ID NO: 1
9. The isolated polynucleotide of Claim 7, wherein said polynucleotide is contained on a recombinant expression vector.
10. The polynucleotide sequence of Claim 9, wherein said expression vector containing said polynucleotide sequence is contained within a host cell.

11. A polynucleotide sequence that hybridizes under stringent conditions to the nucleic acid sequence of SEQ ID NO:1.

12. A method of screening a compound, said method comprising:

- 5 a) providing, in any order:
 i) a peptide comprising at least a portion of the amino acid sequence set forth in SEQ ID NO:4, wherein said portion is capable of binding to a LAT binding ligand;
 ii) a LAT binding ligand; and
10 iii) one or more compounds for screening;
 b) mixing, in any order, said peptide, said LAT binding ligand and said one or more compound; and
 c) measuring the extent of binding of said peptide to said LAT binding ligand.

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13. The method of Claim 12, wherein said LAT binding ligand comprises a tyrosine kinase.

14. The method of Claim 13, wherein said kinase comprises ZAP-70 kinase.

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15. The method of Claim 13, wherein said kinase comprises Syk kinase.

16. The method of Claim 12, wherein said peptide is part of a fusion protein.

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17. A method for detecting the presence of a portion of the polypeptide having the amino acid sequence set forth in SEQ ID NO:4, said method comprising the steps of:

- 30 a) providing in any order:
 i) an antibody capable of reacting with a portion of the polypeptide having the sequence set forth in SEQ ID NO:4; and
 ii) a sample suspected of containing at least a portion of the polypeptide having the sequence set forth in SEQ ID NO: 4;

- b) combining said antibody and said sample under conditions such that a complex is formed between said antibody and said portion of said polynucleotide; and
- c) detecting said complex.

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18. The method of Claim 17, wherein said antibody is a polyclonal antibody.

19. The method of Claim 17, wherein said antibody is a monoclonal antibody.

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20. The method of Claim 17, wherein said sample comprises lymphocytes.

21. A method for detecting the presence of polynucleotide sequences encoding at least a portion of LAT gene in a sample, said method comprising the steps of:

- a) providing in any order:
 - i) a polynucleotide comprising a sequence that hybridizes under stringent conditions to the nucleic acid sequence of SEQ ID NO:1; and
 - ii) a sample suspected of containing nucleic acid comprising the sequence of SEQ ID NO:1;
- b) combining said polynucleotide and said sample under conditions such that a hybridization complex is formed between said polynucleotide and said sample nucleic acid; and
- c) detecting said hybridization complex.

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22. The method of Claim 21, wherein said sample nucleic acid is RNA.

23. The method of Claim 21, wherein said sample nucleic acid is DNA.

24. The method of Claim 21, wherein said sample comprises lymphocytes.

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25. The method of Claim 24, wherein said detected hybridization complex correlates with expression of the LAT gene in said lymphocytes.



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Human Vav Nucleotide Sequence (1-2757)

Figure 11A

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Human Vav Amino Acid Sequence (1-797)

Figure 11B

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Human Cbl Nucleotide Sequence (1-3090)

Figure 12A

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Human Cbl Amino Acid Sequence (1-896)

Figure 12B

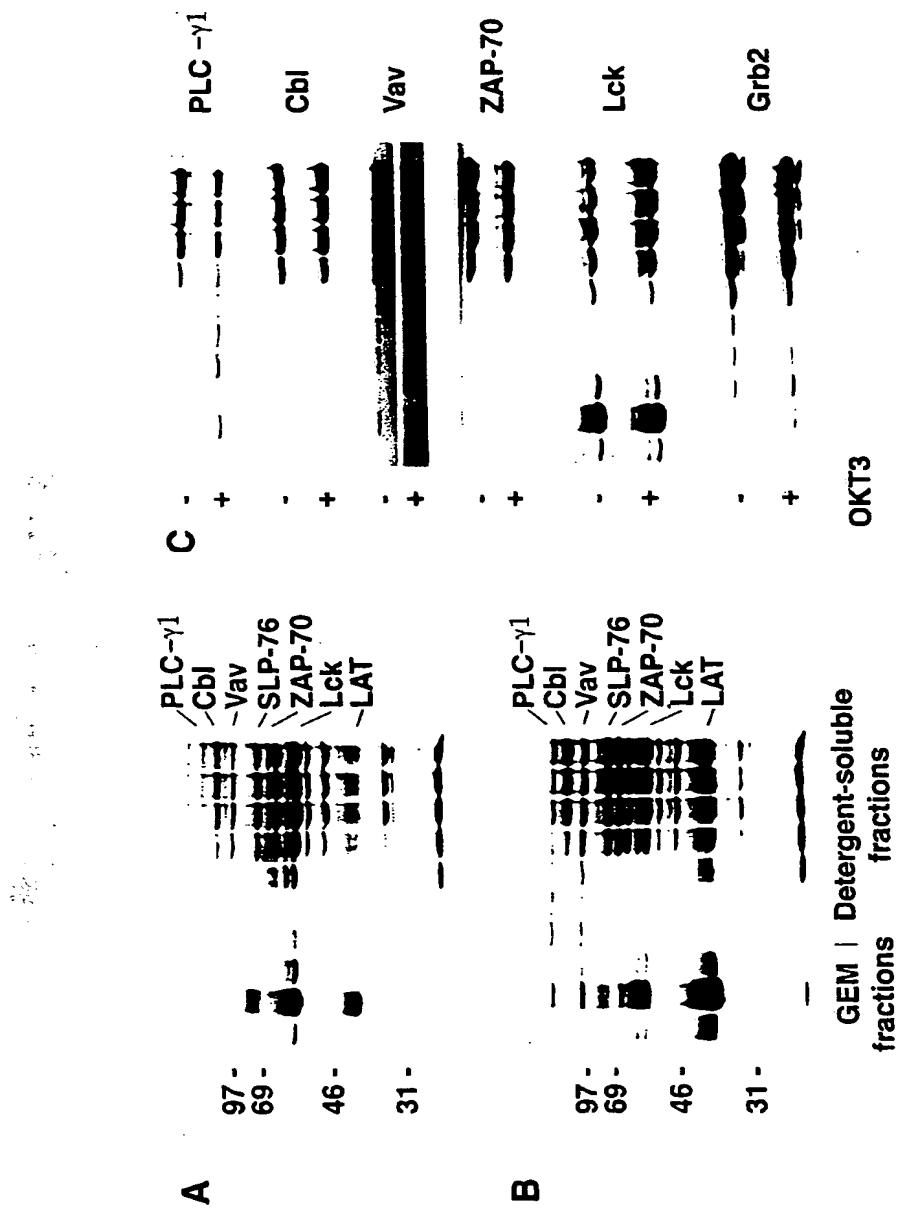


Fig. 13

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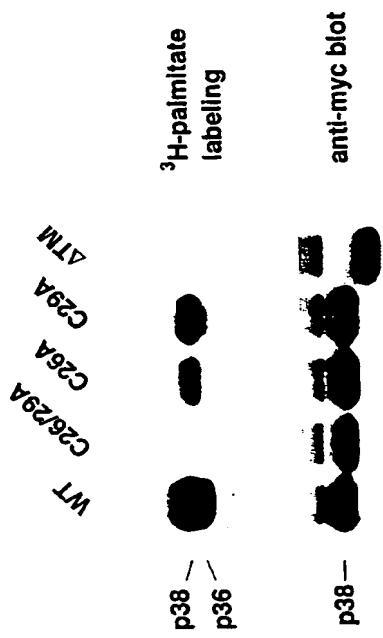


Fig. 14

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23/24

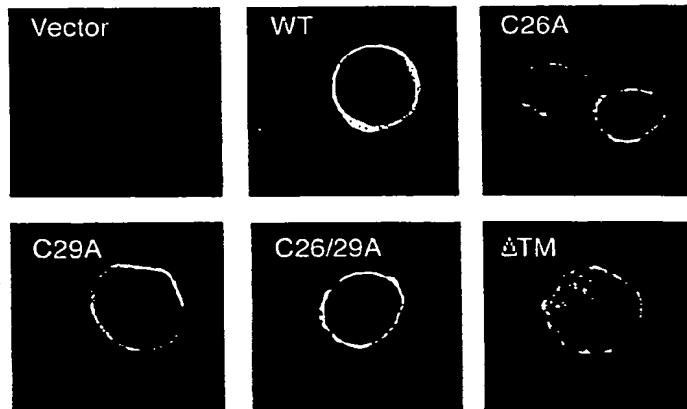
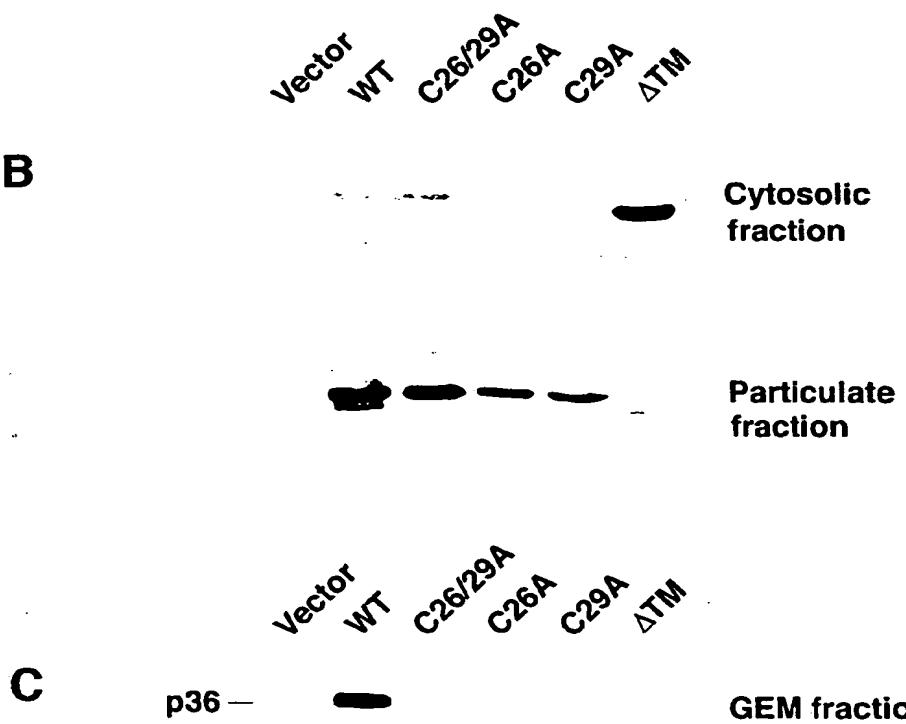
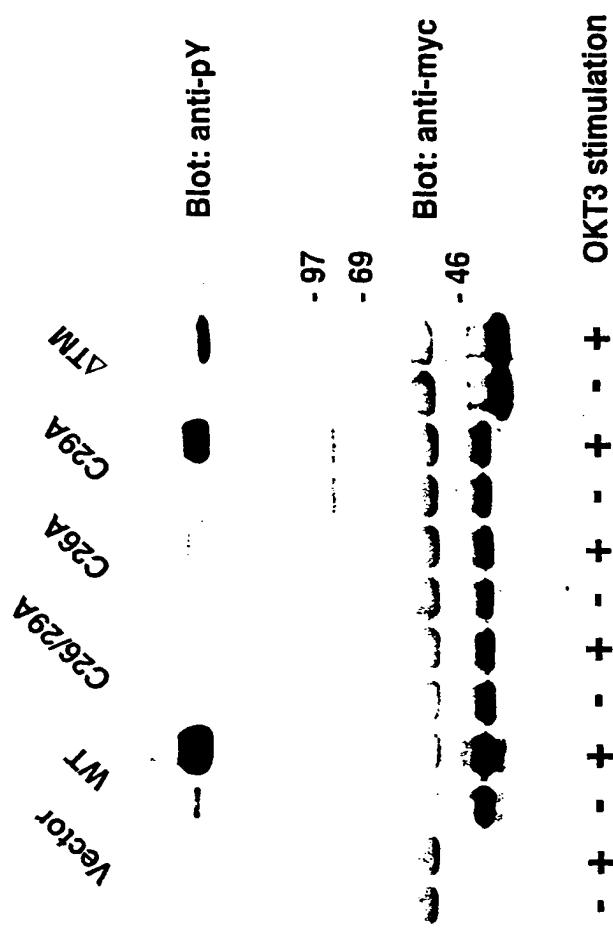
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FIG. 15

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Ile Gln Phe Lys Arg Pro His Thr Val Ala Pro Trp Pro Pro Ala Tyr
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Pro Pro Val Thr Ser Tyr Pro Pro Leu Ser Gln Pro Asp Leu Leu Pro
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 Ile Pro Arg Ser Pro Gln Pro Leu Gly Gly Ser His Arg Thr Pro Ser
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30 <213> Homo sapiens

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 Arg Pro Met Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser Asp
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 Gly Gly Gly Pro Leu His Lys Phe Leu Leu Gly Lys Lys Glu Ile Pro
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 45 Val Ser Asn Val Ala Glu Leu Leu His Gln Val Ala Met Gly Met Lys
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 Tyr Leu Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala Arg Asn
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5 Lys Trp Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg Met Arg
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10 Gly Gly Phe Ala Leu Ser Val Ala His Gly Arg Lys Ala His His Tyr
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15 Thr Ile Glu Arg Glu Leu Asn Gly Thr Tyr Ala Ile Ala Gly Gly Arg
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Thr His Ala Ser Pro Ala Asp Leu Cys His Tyr His Ser Gln Glu Ser
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20 Asp Gly Leu Val Cys Leu Leu Lys Lys Pro Phe Asn Arg Pro Gln Gly
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Val Gln Pro Lys Thr Gly Pro Phe Glu Asp Leu Lys Glu Asn Leu Ile
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25 Arg Glu Tyr Val Lys Gln Thr Trp Asn Leu Gln Gly Gln Ala Leu Glu
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Gln Ala Ile Ile Ser Gln Lys Pro Gln Leu Glu Lys Leu Ile Ala Thr
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30 Thr Ala His Glu Lys Met Pro Trp Phe His Gly Lys Ile Ser Arg Glu
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35 Glu Ser Glu Gln Ile Val Leu Ile Gly Ser Lys Thr Asn Gly Lys Phe
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Val Glu His Tyr Ser Tyr Lys Ala Asp Gly Leu Leu Arg Val Leu Thr
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<p>1999-418926/35 B04 D16 USSH 1997.12.23 US DEPT HEALTH & HUMAN SERVICES *WO 09932627-A2 1997.12.23 1997-068690(+1997US-068690) (1999.07.01) C12N 15/12, C07K 14/705, C12N 15/62, G01N 33/50, 33/53, C12Q 1/68, C07K 16/28</p> <p>Linker for activation of T cell protein used to, e.g. screen for modulators of T cell signaling (Eng)</p> <p>C1999-123167 N(AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW)</p> <p>Addnl. Data: SAMELSON L E, ZHANG W 1998.12.23 1998WO-US27400</p>	<p>B(4-C1G, 4-E2F, 4-G1, 4-N2A, 14-A1, 14-C3, 14-G2A, 14-G3, 14-H1) D(5-H9, 5-H11, 5-H12A, 5-H12D2, 5-H17A6) .8</p> <p>(I) comprises at least part of the 233 amino acid (aa) sequence (S1) (given in the specification), of the human LAT (linker for activation of T cells) protein.</p> <p>INDEPENDENT CLAIMS are also included for the following:</p> <ol style="list-style-type: none"> (1) a purified antibody (Ab) that binds specifically to (I); (2) isolated nucleic acid (II) that encodes (S1), or its complement; (3) method of screening compounds for modulation of interaction between (I) and a LAT-binding ligand; (4) method for detecting (I) by reaction with Ab; and (5) method for detecting (II) by hybridization. <p>ACTIVITY Immunomodulatory; antimicrobial; anticancer; anti-inflammatory; anti-allergic.</p> <p>MECHANISM OF ACTION Modulation of interaction between (I) and the T-cell receptor (TCR) affects the TCR signaling pathway. LAT is a substrate for</p>
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| WO 09932627-A+

<p>tyrosine kinases and becomes phosphorylated after TCR engagement, resulting in recruitment of other signaling molecules.</p> <p>USE (I) is used to identify and test (ant)agonists of tyrosine kinase signaling pathways, i.e. modulation of interaction between tyrosine kinase substrates and intracellular ligands or between these ligands and other members of the pathway, including identification of downstream signaling proteins, particularly in immune system cells. These modulators are potentially useful as drugs and diagnostic agents, particularly for diseases that involve undesirable cell growth, differentiation, proliferation or T cell anergy, e.g. neoplasia, inflammation, hypersensitivity/allergy, microbial infection, metabolic, genetic or autoimmune diseases, graft rejection. (I) is also used to generate specific antibodies, used for detection of LAT. Nucleic acid (II) that encodes (I), or its fragments, are used to identify homologous sequences in other species; to detect the LAT gene and as sources of antisense therapeutics.</p> <p>ADVANTAGE Modulators of (I) are potentially more specific and less toxic than known immunosuppressants such as cyclosporin.</p>	<p>ADMINISTRATION Modulators of (I) are administered parenterally, e.g. at 10-1000 µg/kg.</p> <p>EXAMPLE cDNA encoding human LAT (linker for activation of T cells) protein was fused to a myc tag-encoding sequence, then cloned into pcDNA3 for transfection of 293T cells. Immunoblotting with the anti-myc antibody 9E10 indicated presence of a 40 kDa protein in transfected cells only, showing that the cDNA contained the entire coding region.</p> <p>TECHNOLOGY FOCUS Biotechnology - Preferred Polypeptides: (I) includes at least one tyrosine residue and is particularly aa 28-233 (the cytosolic domain). (S1) has 10 tyrosine residues in the predicted cytosolic domain and 5 potential binding sites for the Grb2 SH2 domain. Preferred Nucleic Acid: (S1) is encoded by a 1059 bp sequence (S2) (given in the specification), and this may be part of an expression vector, optionally present inside a host cell.</p>
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<p>1999-418926/35</p> <p>Preparation: LAT was purified from Jurkat E6.1 cells that had been stimulated with OKT3 ascites, then digested with trypsin and peptide fragments sequenced. The information obtained was used to search the GenBank database and an expressed sequence tag clone (from human fetal heart) identified. A fragment of this clone was used to screen a cDNA library from YT cells and a 1.6 kb fragment identified. It included an open reading frame for (4). LAT mRNA is detected mainly in the thymus and peripheral blood, and at a low level in the spleen. Once isolated, the cDNA can be expressed in vitro or cloned into conventional expression vectors.</p> <p>Biology - Preferred Methods: In method (3), (I), which can bind a LAT-binding ligand (L); (L) and at least one test compound are incubated together and the extent of (I)-(L) binding measured. Particularly (L) is a tyrosine kinase, specifically ZAP-70 or Syk, and (I) is particularly part of a fusion protein. In method (4), Ab is mono- or poly-clonal and the test sample includes lymphocytes. In method (5), the test material is RNA or DNA, particularly from lymphocytes, and detection of a hybridization complex is correlated with expression of the LAT gene in these cells.</p> <p>Preparation: Ab are produced by conventional immunization with LAT</p>	<p>(or its mutants, fragments) and/or cell fusion methods.</p> <p>Organic Chemistry - Preparation: Fragments of LAT, and oligonucleotide fragments of (II), are produced by usual methods of chemical synthesis. (124pp1251DwgNo.0/16)</p>
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| WO 09932627-A/2

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ID AAX89078 standard; DNA; 2758 BP.
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AC AAX89078;
XX
DT 14-SEP-1999 (first entry)
XX
DE Nucleotide sequence of human Vav.
XX
KW LAT; tyrosine kinase; linker for activation of T cell; TCR; human;
KW T-cell receptor; TCR signalling pathway; neoplasia; inflammation;
KW hypersensitivity; allergy; microbial infection; genetic disease;
KW autoimmune disease; graft rejection; modulator; Vav; ss.
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PA (USSH) US DEPT HEALTH & HUMAN SERVICES.
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PI Samelson LE, Zhang W;
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DR WPI; 1999-418926/35.
DR P-PSDB; AAY27125.
XX
PT Linker for activation of T cell protein used to, e.g. screen for
PT modulators of T cell signalling
XX
PS Disclosure; Fig 11A; 125pp; English.

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ID AAY27125 standard; Protein; 797 AA.
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XX
DT 14-SEP-1999 (first entry)
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DE Amino acid sequence of human Vav.
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KW LAT; tyrosine kinase; linker for activation of T cell; TCR; human;
KW T-cell receptor; TCR signalling pathway; neoplasia; inflammation;
KW hypersensitivity; allergy; microbial infection; genetic disease;
KW autoimmune disease; graft rejection; modulator; Vav.
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DR WPI; 1999-418926/35.
DR N-PSDB; AAX89078.
XX
PT Linker for activation of T cell protein used to, e.g. screen for
PT modulators of T cell signalling
XX
PS Disclosure; Fig 11B; 125pp; English.
XX
CC The invention relates to a protein tyrosine kinase substrate LAT (linker
CC for activation of T cells) protein. Modulation of interaction between LAT
CC and the T-cell receptor (TCR) affects the TCR signalling pathway. LAT is
CC a substrate for tyrosine kinases and becomes phosphorylated after TCR
CC engagement, resulting in recruitment of other signalling molecules. LAT
CC is used to identify and test (ant)agonists of tyrosine kinase signalling
CC pathways, i.e. modulation of interaction between tyrosine kinase
CC substrates and intracellular ligands or between these ligands and other
CC members of the pathway, including identification of downstream signalling
CC proteins, particularly in immune system cells. These modulators are
CC potentially useful as drugs and diagnostic agents, particularly for
CC diseases that involve undesirable cell proliferation, differentiation,
CC growth or T cell anergy, e.g. neoplasia, inflammation, hypersensitivity/
CC allergy, microbial infection, metabolic, genetic or autoimmune diseases,
CC graft rejection. LAT is also used to generate specific antibodies, used
CC for detection of LAT. Nucleic acid that encodes LAT, or its fragments,
CC are used to identify homologous sequences in other species; to detect the
CC LAT gene and as sources of antisense therapeutics. Modulators of LAT are
CC potentially more specific and less toxic than known immunosuppressants
CC such as cyclosporin. The present sequence represents the amino acid
CC sequence of human Vav.
XX
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SQ 0 Others;
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